Claim 24 has been amended to recite "wherein said amino acid sequence of said light chain comprises".

Claim 27 has been amended to recite "the amino acid sequence of said heavy chain comprising".

Claim 28 has been amended to recite "wherein said amino acid sequence of said heavy chain comprises".

Support for "complementarity determining region" and "murine Act-1 antibody" is found throughout the specification and in the claims as originally filed. This Amendment adds no new matter.

Additional remarks are set forth below with reference to the numbered paragraphs in the Office Action.

Paragraph 6A. Rejection of Claims 1-9, 18-20, 23-24 and 27-28 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-9, 18-20, 23-24 and 27-28 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in the recitation of "substantially the same". The Examiner states that "substantially the same" is a relative term and that the metes and bounds of the phrase is unclear.

It is noted that "substantially the same" is recited in independent Claims 1, 8, 13 and 18 and not in Claims 23-24 and 27-28.

Independent Claims 1, 8, 13 and 18 have been amended to delete the phrase "substantially the same," obviating the rejection of these claims and claims dependent therefrom on this basis.

Paragraph 6B. Rejection of Claims 8, 9, 11, 12 and 28 Under 35 U.S.C. § 112, Second Paragraph

Claims 8, 9, 11, 12 and 28 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in the recitation of "has the sequence" or "having the sequence" because it is unclear if these phrases are meant to be open or closed language.

It appears that Claims 23-24 and 27 also contain the language objected to by the Examiner. Accordingly, Claims 8, 23-24 and 27-28 have been amended to recite standard transitional phrases, as requested by the Examiner, thereby obviating the rejection.

Paragraph 8. Rejection of Claims 1-4, 6, 8-9, 13 and 18 Under 35 U.S.C. § 102(b) or Under 35 U.S.C. § 103(a)

Claims 1-4, 6, 8-9, 13 and 18 are rejected under 35 U.S.C. § 102(b) as being anticipated by or in the alternative under 35 U.S.C. § 103(a) as being obvious over Bendig *et al.* (U.S. Patent No. 5,840,299). Bendig *et al.* (U.S. Patent No. 5,840,299) issued on November 24, 1998 on an application filed November 21, 1995. The issue date of Bendig *et al.* is more than two years after the filing date of the subject application. Accordingly, Bendig *et al.* is not prior art under 35 U.S.C. § 102(b). However, in making the rejection the Examiner quoted 35 U.S.C. § 102(e) (Office Action, Paragraph 7). Therefore, it appears that the reference to 35 U.S.C. § 102(b) is a typographical error and the rejection under 35 U.S.C. § 102(b) is treated as a rejection under 35 U.S.C. § 102(e).

Bendig *et al.* teaches humanized α4-specific antibodies. The Examiner acknowledges that Bendig *et al.* does not teach antibodies that have binding specificity for α4β7, in accordance with the subject claims. However, in the Examiner's opinion, the antibodies of Bendig *et al.* appear to have binding specificities encompassed by the claims. The Examiner states that it is Applicants' burden to establish a patentable distinction between the claimed and referenced antibodies and methods.

The claims as amended are drawn toward antibodies, heavy chains, light chains and fragments thereof that have binding specificity for α4β7 and that comprise CDRs which have amino acid sequences set forth in the claims. Therefore, the disclosure of antibodies which appear to be able to bind α4β7 without a teaching of the claimed CDRs is insufficient to anticipate or render the claimed invention obvious.

A comparison of the amino acid sequences of the CDRs of murine antibody 21.6 (presented in Figures 6 and 7 of U.S. Patent No. 5,840,299), which are identical to the sequences of the CDRs of the humanized 21.6 antibodies of Bendig *et al.* (with the exception of CDR3 of 21.6 Hc), with the amino acid sequences of the CDRs recited in the claims of the subject application clearly reveals that the instant claims are neither anticipated by or obvious over Bendig *et al.*

Amino Acid Sequences of Light Chain CDRs

CDR1	
murine 21.6	KTSQDINKYMA
residues 44-59 of SEQ ID NO:12	RSSQSLAKSYGNTYLS
CDR2	
murine 21.6	YTSALQP
residues 75-81 of SEQ ID NO:12	GISNRFS
CDR3	
murine 21.6	LQYDNLWT
residues 114-122 of SEQ ID NO:12	LQGTHQPYT

Amino Acid Sequences of Heavy Chain CDRs

CDR1	
murine 21.6	DTYIH
residues 50-54 of SEQ ID NO:15	SYWMH
CDR2	
murine 21.6	RIDPANGYTKYDPKFQG
residues 69-85 of SEQ ID NO:15	EIDPSESNTNYNQKFKG
CDR3	
murine 21.6	EGYYGNYGVYAMDY
21.6 Hc	EGYFGNYGVYAMDY
residues 118-129 of SEQ ID NO:15	GGYDGWDYAIDY

None of the CDR sequences recited in the claims are identical to CDR sequences disclosed in Bendig *et al.* Thus, the claims are not anticipated.

In regard to obviousness, the person skilled in the art could not have altered the amino acid sequences of the CDRs taught by Bendig *et al.* with a reasonable expectation of success of

arriving at the claimed invention. It is noted that the CDR sequences recited in the claims contain amino acid deletions, insertions and non-conservative substitutions relative to the corresponding CDR sequences taught in Bendig *et al.* Furthermore, alignment of the CDR sequences recited in the claims with the corresponding CDR sequences of Bendig *et al.* using Blast 2 Sequences (Tatusova, T. A. *et al.*, *FEMS Microbiol Lett*, *174*:187-188 (1999)) under low stringency (matrix: Blosum62; gap open: 11; gap extension: 1; x_dropoff: 50; expect: 100000; word size: 2; Filter: off), revealed that only the sequences of CDR2 of the heavy chain exhibit any similarity (see Exhibits A-G), and the similarity of the heavy chain CDR2 sequences is limited, with 8 identities, 3 conservative substitutions and 6 non-conservative substitutions over 17 residues (see Exhibit E, note that the algorithm deleted the first residue of each sequence in order to provide an optimal alignment).

In view of these differences, the claimed invention is neither anticipated nor made obvious by the disclosure of Bendig *et al.* Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(e) or 35 U.S.C. § 103(a) is requested.

Paragraph 9. Rejection of Claims 1-9, 18-20, 23-24 and 27-28 Under 35 U.S.C. § 103(a)

Claims 1-9, 18-20, 23-24 and 27-28 are rejected under 35 U.S.C. § 103(a) as being obvious over Queen *et al.* (U.S. Patent No. 5,530,101) in view of Lazarovits *et al.* (*J. Immunol.*, *151*:6482-6489 (1993)) and in further evidence by the "Information for Contributors" of volume 151 of the *Journal of Immunology*.

As stated in the record, the Examiner believes that motivation for combining or modifying the teachings of the cited references is found in the references themselves or in knowledge generally available to one of skill in the art (Office Action dated 3/13/98 (Paper 12), at page 4). The Examiner further states that, given the knowledge in the art of the success of antibodies specific for adhesion molecules acting as antagonists and inhibiting inflammation *in vivo*, one of ordinary skill would have been motivated to generate a humanized anti-$\alpha 4\beta 7$ antibody. The Examiner further states that a rejection under 35 U.S.C. § 103 only requires that there be a reasonable expectation that the humanized anti-$\alpha 4\beta 7$ antibody would be successful in therapy of human patients (Paper 12, at page 5, lines 8-13).

Applicants maintain that the rejection is improper because there is no motivation to combine the Queen *et al.* and Lazorovits *et al.* references and the combination does not provide the necessary reasonable expectation of success. As stated in the record, Lazarovits *et al.* teaches

the possible benefit of interfering with α4β7 for immunotherapy of rheumatoid arthritis, but does not suggest the use of Act-1 for this purpose. Queen *et al.* teaches general methods for humanization of antibodies, but does not suggest humanization of Act-1.

It appears that the Examiner has not considered that the binding of an antibody to a cell surface molecule (e.g., an adhesion molecule) can have unpredictable effects on the activity of the molecule. The Examiner assumes that the Act-1 antibody would inhibit the activity of α4β7 and thereby prevent cellular adhesion mediated by binding of α4β7 to ligand. However, it is well known that antibodies can activate, promote or have no effect on the activity of a protein upon binding thereto. Further when a protein, such as a an adhesion molecule, binds to more than one ligand, an antibody that binds the protein can inhibit binding to one ligand while simultaneously promoting binding to another ligand. Thus, the administration of an antibody that binds to a cell adhesion molecule (e.g., α4β7) to a human could induce or exacerbate the disease it is administered to treat.

The art of record clearly demonstrates that the person of skill in the art would not have considered the Act-1 antibody to be a potential therapeutic agent. Schweighoffer *et al.* (*J. Immunol.*, *151*:711-729 (1993); Reference AW of record) teaches that α4β7 binds to both fibronectin and vascular cell adhesion molecule-1 (VCAM-1). The reference also describes the results of a study in which the ability of Act-1 to affect the binding of $\alpha4\beta7^+$ cells to fibronectin or VCAM-1 was assessed in *in vitro* cellular adhesion assays. The results of the study clearly demonstrate that Act-1 inhibits adhesion of $\alpha4\beta7^+$ cells to fibronectin, but augments adhesion of $\alpha4\beta7^+$ cells to VCAM-1 (see Schweighoffer *et al.*, at Abstract and Figure 6). The skilled person would have concluded, based upon the teachings of Schweighoffer *et al.*, that administration of Act-1 to inhibit binding of $\alpha4\beta7^+$ cells to fibronectin would necessarily augment binding of $\alpha4\beta7^+$ cells to cells expressing VCAM-1.

The Examiner relies on Lazarovits *et al.* as establishing motivation to use Act-1 to treat rheumatoid arthritis in humans. However, the person skilled in the art at the time the invention was made would have evaluated the teaching of Lazarovits *et al.* in light of the teachings of Schweighoffer *et al.* In addition to suggesting that interference with α4β7 may be beneficial in the immunotherapy of RA, Lazarovits *et al.* teaches that both fibronectin and VCAM-1 are up-regulated in rheumatoid synovium (Lazarovits *et al.*, *J. Immunol.*, 151:6482-6489 (1993); Abstract). Accordingly, the skilled person would have concluded based on the teachings of Lazarovits *et al.* and Schweighoffer *et al.*, that administration of Act-1 to treat rheumatoid

arthritis would induce or exacerbate disease by augmenting α4β7/VCAM-1 mediated infiltration of T cells into the synovium. The authors of Lazarovits *et al.* were clearly mindful of the teaching of Schweighoffer *et al.* (Andrew I. Lazarovits coauthored both publications) and accordingly did not endorse or suggest using Act-1 as a therapeutic agent. In fact, the combination of Schweighoffer *et al.* and Lazarovits *et al.* results in a teaching away from the invention.

The prior art does not provide a reasonable expectation that Act-1 could successfully be used as a therapeutic agent to treat disease or that any advantage could be realized by producing a humanized Act-1. Accordingly, the person of skill in the art at the time the invention was made would not have been motivated to try to produce a humanized Act-1 antibody using the methods of Queen *et al.* or any other methods. In addition, neither of the cited references discloses the CDR amino acid sequences recited in the claims. Therefore, the claimed invention is not obvious over the combined teachings of the cited references.

The Examiner further states that the Act-1 antibody/hybridoma appears to have been available to others at the time the invention was made. The Examiner bases his conclusion on his observation that the authors of Lazarovits *et al.* (*J. Immunol., 151*:6482-6489 (1993)) and Lazarovits *et al.* (*J. Immunol., 133*:1857-1862 (1984); Reference AS of record) which describe the making and use of Act-1 are not inventors of the claimed invention. The Examiner further cites "Information for Contributors" of volume 151 of the *Journal of Immunology* (J.I.) as evidence that the Act-1 antibody/hybridoma was available to others at the time the invention was made.

The rejection is based on the assumption that the Act-1 hybridoma was publicly available, and that, using a variety of procedures known in the art, the person of ordinary skill would have a reasonable expectation of success of cloning the rearranged variable regions and of producing humanized antibodies, heavy chains, light chains and fragments thereof in accordance with the claims. Relying as it does upon cloning of rearranged variable regions encoding the murine Act-1 antibody, the rejection hinges upon the public availability of the Act-1 hybridoma.

In this regard, the Examiner cites the publication policy of the J.I. ("Information for Contributors" of volume 151 of the *Journal of Immunology*) as evidence that authors are expected to provide unique materials to qualified investigators. From this information, the Examiner has drawn a presumption of public availability of the murine Act-1 hybridoma cell line. This presumption is improper.

The Examiner relies on only a portion of the statement regarding availability of unique materials from the "Information for Contributors" of the J.I. as evidence of public availability of the Act-1 hybridoma. In so doing, the Examiner has misconstrued the plain meaning of the J.I. policy. The "Information for Contributors" states:

> "Since it is the policy of the AAI that manuscripts are accepted for publication with the understanding that the results are verifiable, authors are expected to provide unique materials to qualified investigators" ("Information for Contributors," *J. Immunol.*, *151* (1993); left hand column, lines 28-31) (emphasis added).

It is clear that The American Association of Immunologists (AAI, publishers of the *Journal of Immunology*) expect that only unique materials which are necessary to verify results reported in the journal will be made available to qualified investigations. Authors who publish in the *Journal of Immunology* are not obligated to make all materials referred to or described in a publication available or to make unique materials available for any purpose other than verification of published results. For example, in the cited Lazarovits *et al.* reference, the Act-1 antibody was used to identify $\alpha 4\beta 7^+$ T cells in the synovial fluid and synovial tissue of patients with RA by immunohistochemistry using Act-1 and secondary reagents (goat anti-mouse IgG-FITC, biotinylated horse anti-mouse IgG and avidin-biotin-peroxidase complex) (Lazarovits *et al.*, *J. Immunol.*, *151*:6482-6489 (1993) at page 6484 under the heading Immunoperoxidase analysis of rheumatoid synovium). Verification of these results would only require that a small sample of the Act-1 antibody be provided. Thus, the cited references do not create a presumption that the Act-1 hybridoma was publicly available at the time the invention was made.

The instant case is analogous to In re LeGrice, 133 U.S.P.Q. 365 (C.C.P.A. 1962), which is discussed in section 2121.03 of the M.P.E.P (7^{th} edition, July 1998). In that case, the court held that catalogues, which were published more than one year before Applicant's filing date, which showed color pictures of the claimed roses, and disclosed that Applicant had raised the roses, did not place the roses in the public domain. The photograph failed to enable, as plant material from the rose described was needed to reproduce the roses asexually. The instant case involving unique cell lines is similar. The claimed humanized antibodies, heavy chains, light chains and fragments thereof are not enabled by the reference to murine antibody Act-1.

The instant case can also be distinguished from Ex parte Thomson, 24 U.S.P.Q.2d 1618 (B.P.A.I. 1992), also cited in M.P.E.P. § 2121.03. In that case, the cited publications themselves established that the seeds at issue were commercially available. Quoting from the cited publications, the Board stated:

> Duff writes "[t]aking the better part of 10 years to develop, Siokra was introduced to the market place for the 1985-86 growing season" and that a Michael Thomas explained that "`the whole industry switched to DPL90' or Siokras for the 1985-86 growing season."

Id. at 1620. The court also quoted an article quoting the inventor Thomson as stating:

> One of the two new cottons being grown this season is our (CSIRO) variety, Siokra. Although Siokra was made available to Cotton Seed Distributors (CSD) for seed increase three seasons ago, and is now being grown commercially on substantial areas . . .

Id. In the face of express statements regarding public availability, the Board found it reasonable to conclude that, "at the time the cited articles were published, skilled artisans throughout the world would have found Siokra seeds readily available on the open market." Id. However, in contrast to the disclosures in Thompson, which expressly indicated public availability, the disclosures of Lazarovits *et al.* (*J. Immunol., 151*:6482-6489 (1993)) and Lazarovits *et al.* (*J. Immunol., 133*:1857-1862 (1984); AS), in view of "Information for Contributors" for J.I., does not constitute evidence supporting public availability of the hybridoma cell line.

Similarly, the fact that the inventive entity of the subject application does not include the authors of the publications which describe the making and use of murine Act-1 antibody does not create a presumption of public availability of the Act-1 hybridoma. The hybridoma was produced by Dr. Andrew I. Lazarovits while he was working as a research fellow in the laboratory of Dr. Robert B. Colvin at Massachusetts General Hospital. LeukoSite, Inc., Assignee of the subject application, obtained the Act-1 hybridoma through a licensing agreement with The General Hospital Corporation, employer of Drs. Lazarovits and Colvin at the time the Act-1 antibody was made.

The record does not contain any evidence which indicates that the Act-1 hybridoma was made available to others or that the authors of the cited references were under any obligation to make the Act-1 hybridoma freely available to others at the time the invention was made. Consequently, no *prima facie* case of public availability has been made out.

Even if, for the sake of argument, the Act-1 antibody/hybridoma were publically available at the time the invention were made, the claimed invention would not be obvious. As discussed above, the combined teachings of the cited references, in view of the entire record, fail to provide a reasonable expectation that Act-1 could successfully be used as an *in vivo* therapeutic or that

any advantage could be gained through the preparation of a humanized Act-1. Consequently, motivation to clone the rearranged variable regions and prepare a humanize Act-1 is lacking.

Moreover, the claimed humanized antibodies possesses unexpected properties which make them unobvious. Provided herewith is a Declaration of Steven B. Landau, M.D. under 37 C.F.R. § 1.132 (Declaration), which describes a Phase I clinical study of LDP-02 (described in Examples 2-4 of the application), a humanized antibody comprising the CDRs of the Act-1 antibody. The study revealed that LDP-02 has unexpected pharmacokinetic and pharmacodynamic properties. For example, no free $\alpha4\beta7$ binding sites (i.e., LDP-02 epitopes) were detected for about two weeks following a single administration of LDP-02 at the lowest dose tested (0.15 mg/kg)(see Declaration at the Figure). *Administration of LDP-02 at higher doses (e.g., 2.5 mg/kg) resulted in saturation of $\alpha4\beta7$ that persisted for up to 70 days (about four half lives).* The remarkably persistent saturation of $\alpha4\beta7$ by LDP-02 has a relationship to the pharmocokinetic half life of the antibody after a single administration (14-17 day *in vivo* half life when administered at 1.5 mg/kg or 2.5 mg/kg; see Declaration at Table 2 (t 1/2z)). The pharmacodynamic effect of maximal saturation up 70 days in combination with pharmacokinetics results was unexpected and could not have been predicted at the time the invention was made.

Further evidence of the unexpected nature of the pharmacodymamic properties of LDP-02 is provided by the original design of the study itself. The study was originally designed to include blood sampling up to study day 36. However, as $\alpha4\beta7$ saturation was still observed at this time point, the study was extended to include blood sampling up to day 212, when the amount of free $\alpha4\beta7$ sites on lymphocytes returned to pre-dose levels. The unexpected results of the study indicate that LDP-02 may be therapeutically administered as a single dose at intervals of 2 weeks to 2 months or more in order to provide effective treatment.

A determination of patentability under 35 U.S.C. § 103 requires that the entire record as a whole, including objective evidence, be considered. Reconsideration and withdrawal of the rejection are respectfully requested.

Supplemental Information Disclosure Statement

A Supplemental Disclosure Statement under 37 C.F.R. § 1.97(c) is being filed concurrently with this Amendment. Consideration of the information cited therein is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call Helen E. Wendler, Esq. at (781) 861-6240.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Robert H. Underwood

Robert H. Underwood
Registration No. 45,170
Telephone (781) 861-6240
Facsimile (781) 861-9540

Lexington, Massachusetts 02421-4799

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